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Synthesis of Tropane Derivatives

Abdalmajeed Salih Hamad Alsamarrai

Abstract

This chapter refers to tropane alkaloid compounds best known for their occurrence, biosynthesis, and pharmacological properties in a subsection of the plant family Solanaceae including the *Atropa*, *Duboisia*, *Hyoscyamus*, and *Scopolia* species, together with their semisynthetic derivatives. Tropane alkaloids are useful as parasympatholytics that competitively antagonize acetylcholine. The bicyclic ring of tropane moiety forms the base of these alkaloids, and the largest number of tropane alkaloids is substituted on the atom C-3 of the tropane ring in the form of ester derivatives. Also, this chapter provides routes to previous methods for synthesizing tropane-2-yl derivatives as well as new routes to synthesize 2-(*p*-toluenesulphonyl) tropane-2-ene (anhydroecgonine). The new strategy for synthesizing anhydroecgonine might be helpful to adopt the best method of synthesizing tropane-2-yl derivatives.

Keywords: alkaloids, tropane, ecgonine, cocaine, tropinone, tropidine

1. Introduction

1.1 Tropane alkaloids occurrence

Tropane alkaloids (**Figure 1**) are among the oldest medicines known to men. A secondary metabolites containing the tropane nucleus constitute one of the largest and most important group of naturally occurring compounds [1]. Secondary metabolites of Solanaceae plant, sharing tropane skeleton (1) as a common structural feature can be divided into two classes: tropine (2) and ecgonine (3) derivatives [2]. The first group is represented by atropine from *Atropa belladonna* (4) and scopolamine (5) (*Scopola carniolica*) which are considered to be anticholinergic drugs. The second includes one of the strong stimulants and mostly used as a recreational drug, cocaine (6).

Over 600 naturally occurring alkaloids of tropane can be found in plants such as *Datura stramonium* [3]. Cocaine (6) was first isolated from *Erythroxylon coca* in 1860 [4–7] and is still a prolific field of research. Although alkaloids with the tropane moiety are the oldest medicines known to man, they are still a subject of continual review in the chemical literature, and only recently they have been isolated, purified, and studied [8, 9].

1.2 Biosynthesis of tropane alkaloids

Alkaloids possess quite complex structures, and the study of biosynthesis of these alkaloids has a long history. It is generally thought that the tropane moiety arises from complex enzymatic processes involving phytochemical precursors.

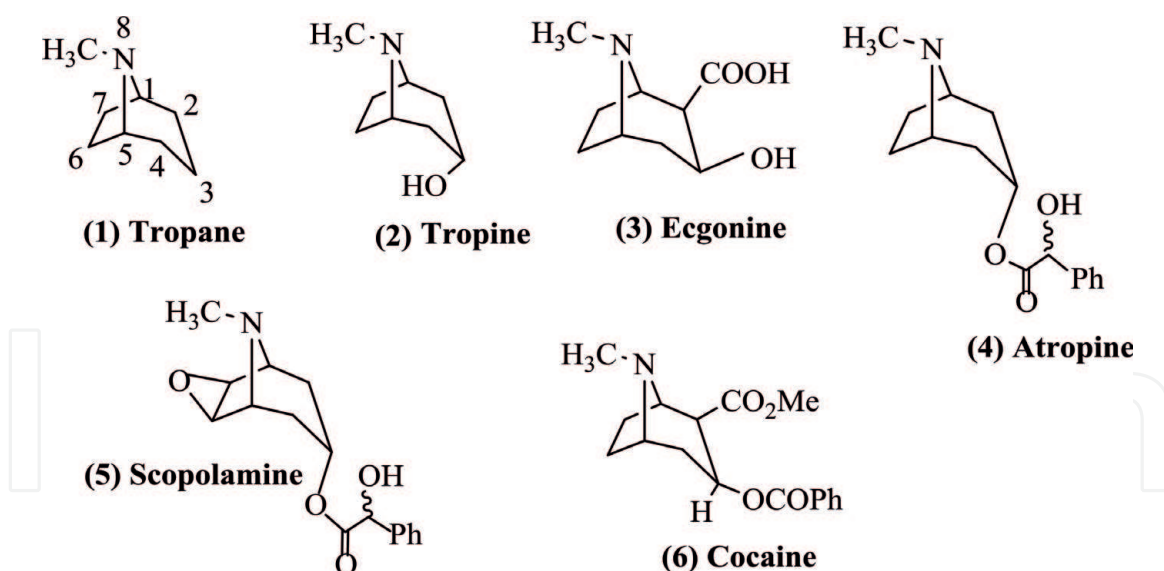


Figure 1.
Some tropane alkaloids.

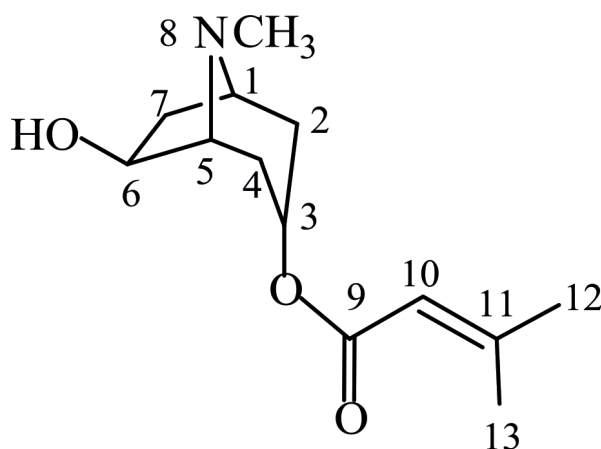


Figure 2.
3α-seneciolyloxy-6β-hydroxytropane.

Incorporation of radioactive labeled precursors has eased monitoring pathway on which the tropane derivatives are formed [10]. Recent studies making use of labeled ornithine (7), *N*-methylornithine (8), and 1,4-butanediamine (9) prepared biosynthetically, have firmly established these precursors and representative examples of complex tropane alkaloids found in Solanaceae plant [11]. After the establishment of the origins of these precursors, attention has been directed mainly toward those alkaloids which, in addition to the tropane residue, contain a 9- or 10-carbon atom unit such as 3 α -seneciolyloxy-6 β -tropane (see **Figure 2**). These units exist in many variant forms, but certain recurrent features led to the belief that many variants have a common phytochemical precursors, for instance, L-ornithine (7) is believed to be converted to diamine (9) by specific enzyme such as hyoscyamine-6 β -hydroxylase (H6H) and the former (9) is considered the precursor in biosynthesis of the bicyclic [3.2.1] skeleton of tropane alkaloids which is outlined in **Figure 3**.

It has been found that oxidation of tropane ring can be achieved by molecular oxygen in the presence of ferrous ions. Also, it has been found that these keto forms of tropane can be catalyzed by an enzyme called reductase [12]. For instance, the biosynthesis pathway to tropane alkaloids, tropinone (10), is reduced by reductase to tropine (2), as it can be seen in **Figure 4**.

Structural assignments of tropane molecules have exhibited difficult problems, and, as a result, progress in their endeavors has been closely associated with

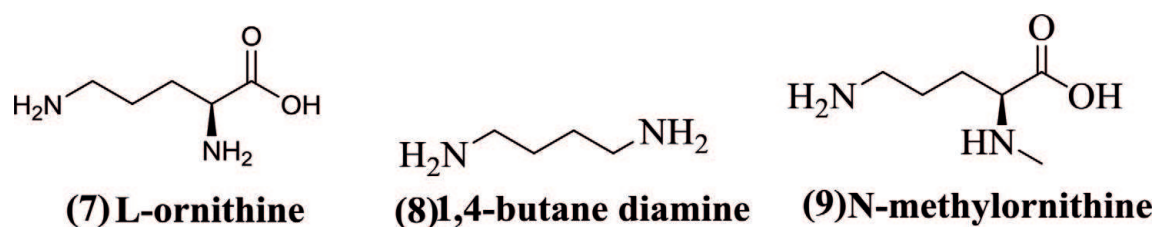


Figure 3.
Amino acids precursors in the biosynthesis of tropane skeleton.

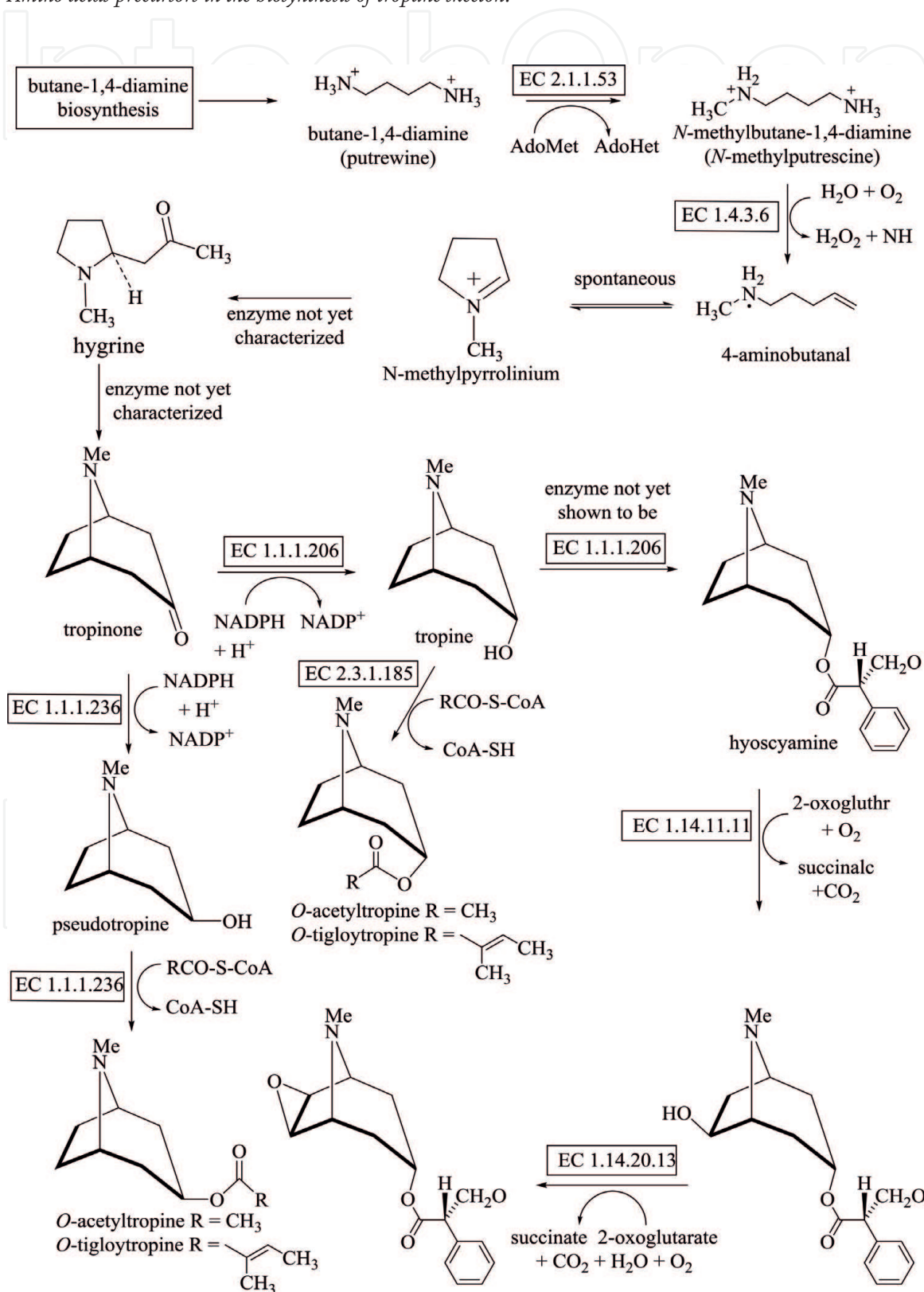


Figure 4.
Bio-synthesis of tropane alkaloids-Alcheetron.com-760 × 570.

development of modern analytical techniques of spectroscopy, of which mass spectroscopy deserves particular mention such as ESI MS, GC-MS, HPLC-MS, and MALDI MS.

1.3 Pharmacological properties of tropane alkaloids

Concerning the pharmacological effects, these compounds are so important because of their pharmacological properties [13]. Alkaloids such as atropine (4), scopolamine (5), and cocaine (6) and their derivatives are best recognized to have pharmacological actions related in the body to the function of neurotransmitter acetylcholine [14]. Some tropane alkaloids can act as anticholinergic effects or stimulants [15]. Pharmaceuticals of tropane derivatives are economically important. Over 20 active pharmaceutical ingredients containing tropane moiety in their structures are manufactured and used as antispasmodics, anesthetic, and mydriatics (see **Figure 5**) [16].

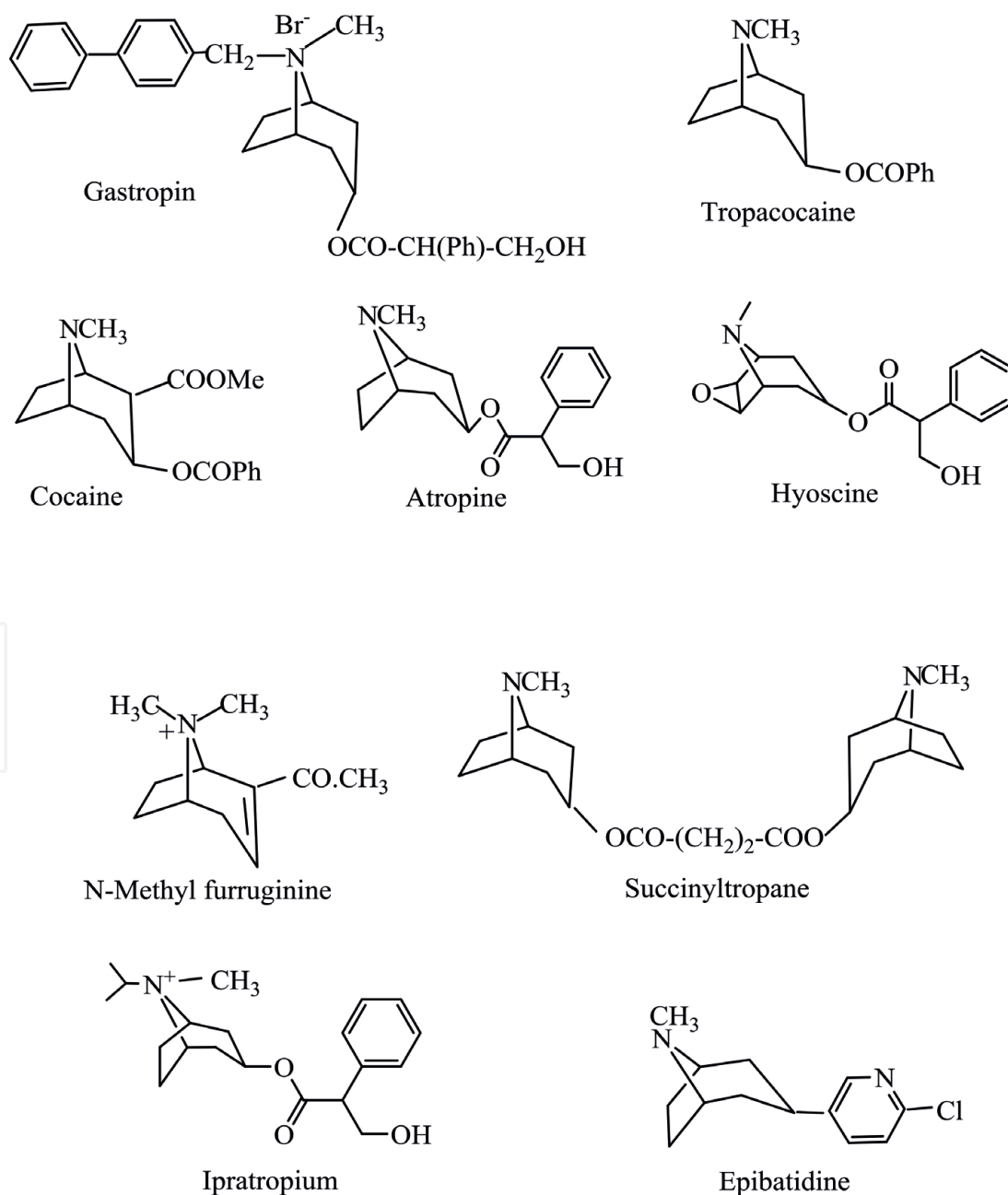


Figure 5.
Some pharmaceutical ingredients containing tropane moiety.

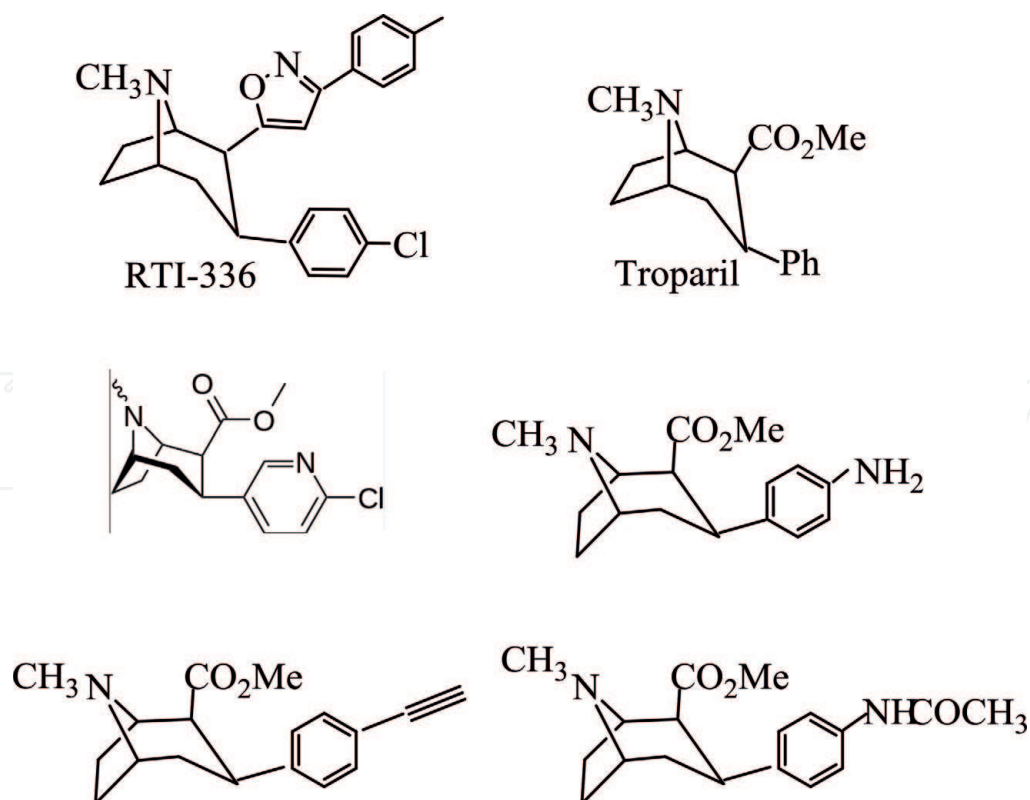


Figure 6.
Some phenyl tropane compounds.

Tropane does not occur naturally in free forms. The favored forms of tropane in plant species are the esters forms. These esters are generally secondary metabolites of the plant species. Tropane esters were isolated from different plant families like Proteaceae, Rhizophoraceae, Euphorbiaceae, and Convolvulaceae, and they are well known to occur in Solanaceae. Most tropane alkaloids in the Solanaceae family arises from the esterification of acids, such as acetic acid, propanoic acid, isobutyric acid, isovaleric acid, 2-methylbutyric acid, tifilic acid (+)- α -hydroxyl- β -phenylpropionic acid, tropic acid, and atropic acid with various hydroxytropans (α -tropane-diol or α -tropane-triol) [5]. Almost all of the tropane-based pharmaceuticals are natural or semisynthetic esters [5, 17, 18]. There are also alkylated or arylated tropane compounds known as phenyltropane (**Figure 6**).

2. Chemistry of tropane alkaloid synthesis routes

Although there are many synthetic routes, Robinsons one-pot synthesis of tropane and its derivatives designed in 1917 [19] is still the best choice for the synthesis of such compounds. The parameters have been changed from time to time in order to increase yield to synthesize a specific derivative (**Figure 7**).

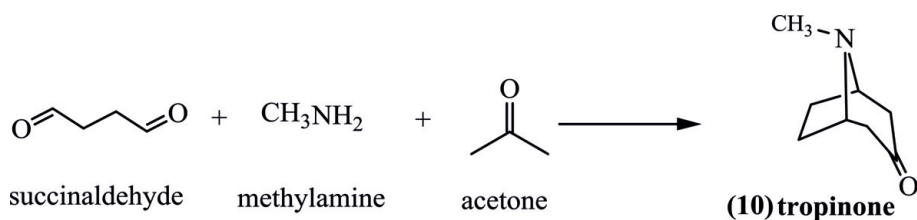


Figure 7.
Robinson's one pot synthesis of tropinone (10).

2.1 Synthesis of tropan-2-yl derivatives

The naturally occurring alkaloid, cocaine (6), possesses a functional group at C-2 in the tropane ring system, which has been modified to give various 2-aminotropanes. Willstatter [20], in his work devoted to the elucidation of the structure of ecgonine (3), obtained the amide (11) which it degraded by Hofmann reaction to 2 α -aminotropane (12) (the α -configurations retained throughout this sequence can be assigned for later work) (**Figure 8**) [21].

Willstatter also obtained (12) by Curtius reaction of the ester (13), and this reaction has been used earlier by Fodor [22] to obtain the amino alcohols (14) and (15), although, again, the configurations at C-2 and C-3 were not known when the work was carried out (**Figure 9**).

Apart from these isolated examples, the most consistent interest in 2-substituted tropanes was shown in connection with the alkaloid dioscorine (16), which was for some time thought to have structure (17) and therefore to be related to tropan-2-one (18). This ketone is an optically active form, which was first prepared by Bell and Archer from ecgonine (3) (**Figure 10**) [23].

The action of phosphoryl chloride on ecgonine (3) was shown by Einborn to give the acid chloride of anhydroecgonine (19) [24]. Bell and Archer converted the crude acid chloride directly to the corresponding amide (20), from which L-(+)-tropan-2-one (18) was obtained in fair yield by Hofmann reaction (**Figure 11**).

When this material was compared with the ketone obtained by degradation of dioscorine (16), the two could not be distinguished [25], and it was left to Pinder and his co-workers to prove that dioscorine was not in fact a tropane derivative [26]. Pinder found that tropidine (21) reacts with the more usual peracid oxidizing

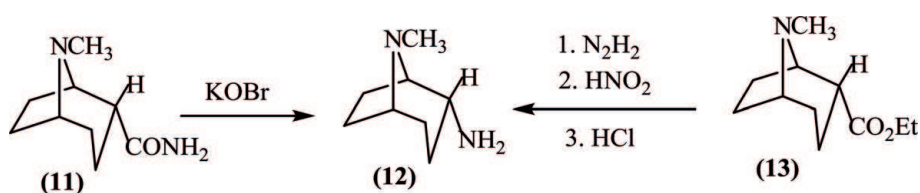


Figure 8.
Hofmann of the amide (11) to the (12).

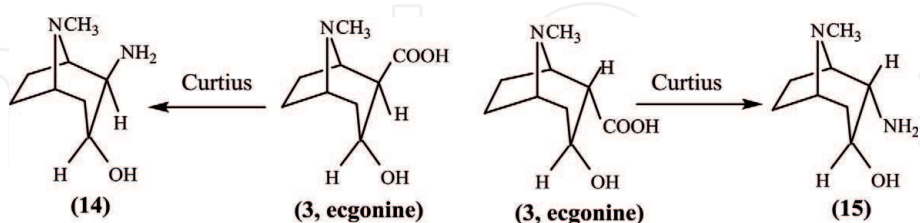


Figure 9.
Curtius reduction of ecgonine to amino alcohols (14) and (15).

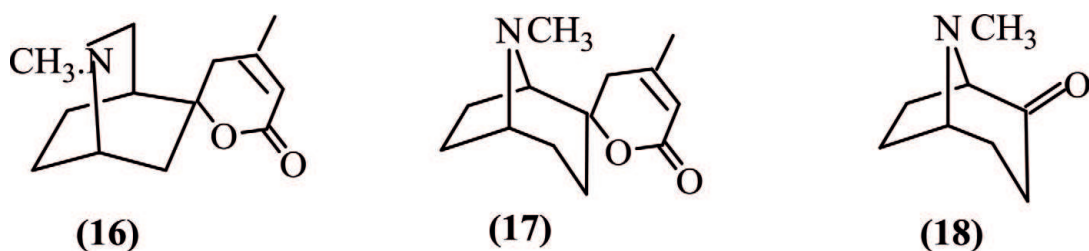


Figure 10.
Some 2-substituted tropane alkaloids.

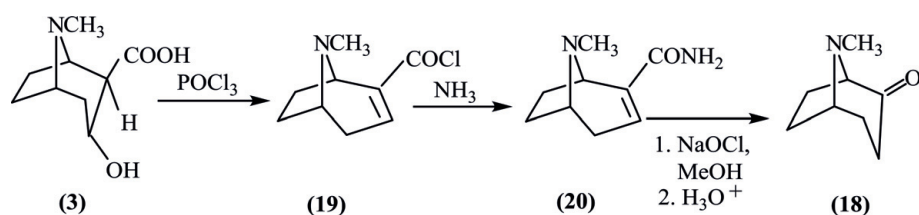


Figure 11.
 Synthesis of tropine-2-one.

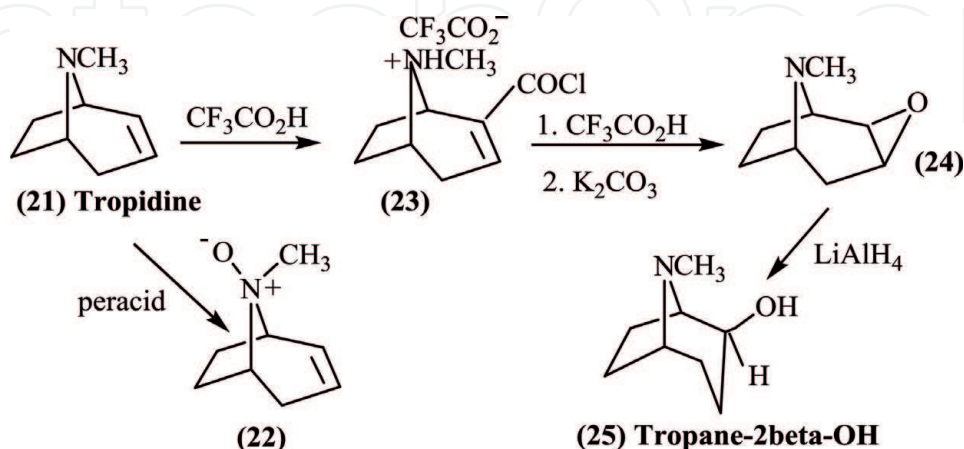


Figure 12.
 Synthesis of tropine-β-ol (25).

agents to give the N-oxide (22), and in acid solution no reaction took place [27]. However, the action of trifluoroperacetic acid on tropidine trifluoroacetate salt (23) gave the 2β,3β-epoxide (24). Reduction of the epoxide with lithium aluminum hydride yielded tropan-3-β-ol (25), but it was found impossible to oxidize this amino alcohol to tropan-2-one (18) (**Figure 12**).

A synthesis of the desired ketone was eventually achieved by a larger route. Treatment of 2-ethoxycarbonyl-pyrrole (26) with phosphoryl chloride and dimethylformide yielded the two isomeric aldehydes, (27) and (28), which were separated fairly easily by fractional distillation in vacuum. Thereafter the crucial stage, a Dieckmann cyclization, led to the β-ketoester (29), which hydrolyzed and was decarboxylated to tropan-2-one (18), outlined in **Figure 13** [26].

Pinder resolved the racemic product into its optically active components and discovered that (+)-tropan-2-one (18) was quite different from the ketone derived from the alkaloid dioscorine (16). With this demonstration that dioscorine (16) was not a tropane derivative, the interest in 2-substituted tropanes diminished, and few papers concerned with these compounds have appeared since 1962.

Tropane-2-one (18) is a convenient source of both tropan-2-αβ-ols. Reduction of the ketone with lithium aluminum hydride yields tropan-2-α-ol (25), which is the expected, equatorial product [23, 26]. Reduction of a cyclic ketone with sodium alcohol mixtures also usually gives the thermodynamically more stable, equatorial alcohol [28], but with sodium in propan-2-ol, pentan-3-ol, tropan-2-one gave mixtures of tropan-2β-ol (30) and tropan-2α-ol (25) [23] (**Figures 13** and **14**). Moreover, when the ratio of alcohol to alkoxide ion at the end of the reaction was increased, the product was found to contain increasing amounts up to 90% of tropan-2β-ol (30). These facts suggested that the axial alcohol (25) is more stable thermodynamically, and this was confirmed by subjecting the pure equatorial isomer (25) to equilibration by means of sodium 2-pentoxide in pentan-3-ol containing 10% fluorenone: the equilibrium mixture contained 85% of the axial isomer (25) [23].

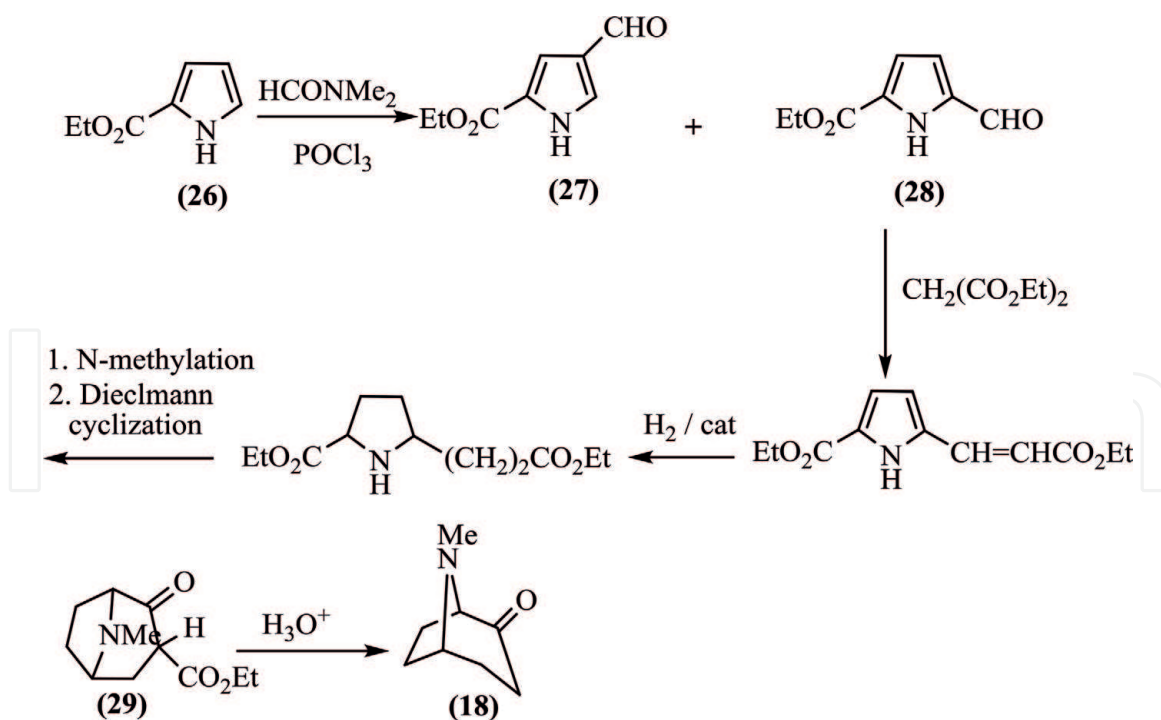


Figure 13.
Synthesis of tropane-2-one (18).

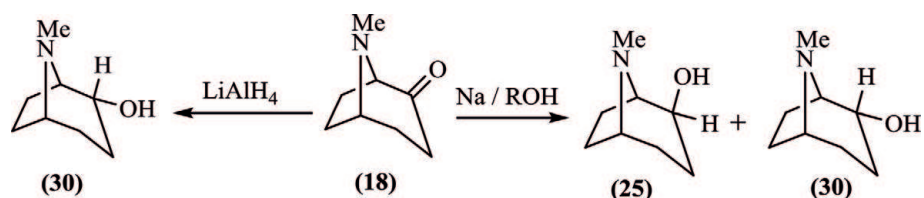


Figure 14.
Synthesis of tropane-2-ol (30).

This reversal of the usual axial equatorial stability relationship may be attributed to the presence of strong, intramolecular hydrogen bonding between the axial hydroxyl group and the nitrogen bridge (31). When the possibility of hydrogen bond formation is removed, as in the anions (32) and (33), the equatorial configuration becomes more stable. When the ratio of free alcohol to alkoxide ion at the end of the sodium alcohol reduction is large, the equilibrium will be mainly between the two alcohols (25) and (30); in these conditions, the product will contain a high proportion of the more stable, axial alcohol. Conversely, when the final proportion of alkoxide ion in the reaction mixture is high, a significant equilibrium between anions (32) and (33) will exist, and the product will contain a higher proportion of the equatorial alcohol (30), arising from the more stable anion (32) (**Figure 15**). These stability relationships enable a useful control of the product ratio to be exercised.

Two further preparations, of 2-halotropanes, are worthy of note. Nickon found that the addition of 1 molar equivalent of bromine to a methanolic solution of tropinone (10) yielded a granular complex, which rearranged to 2 β -bromotropinone (34), by spontaneous transition under ether or by acid catalysis [29]. Earlier, Hobson and Riddell obtained 2 β -chlorotropane (36) by decomposition of the *N*-chloramine (35) in the presence of silver ion (**Figure 16**) [30, 31]. The identical chlorotropane was also obtained by chlorination of the mine hydrochloride, followed by cyclization of the dichloride (37).

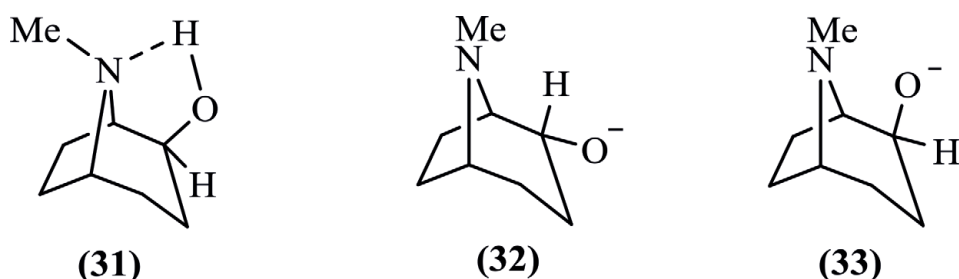


Figure 15.
 The stability relationship of the products (25) and (30).

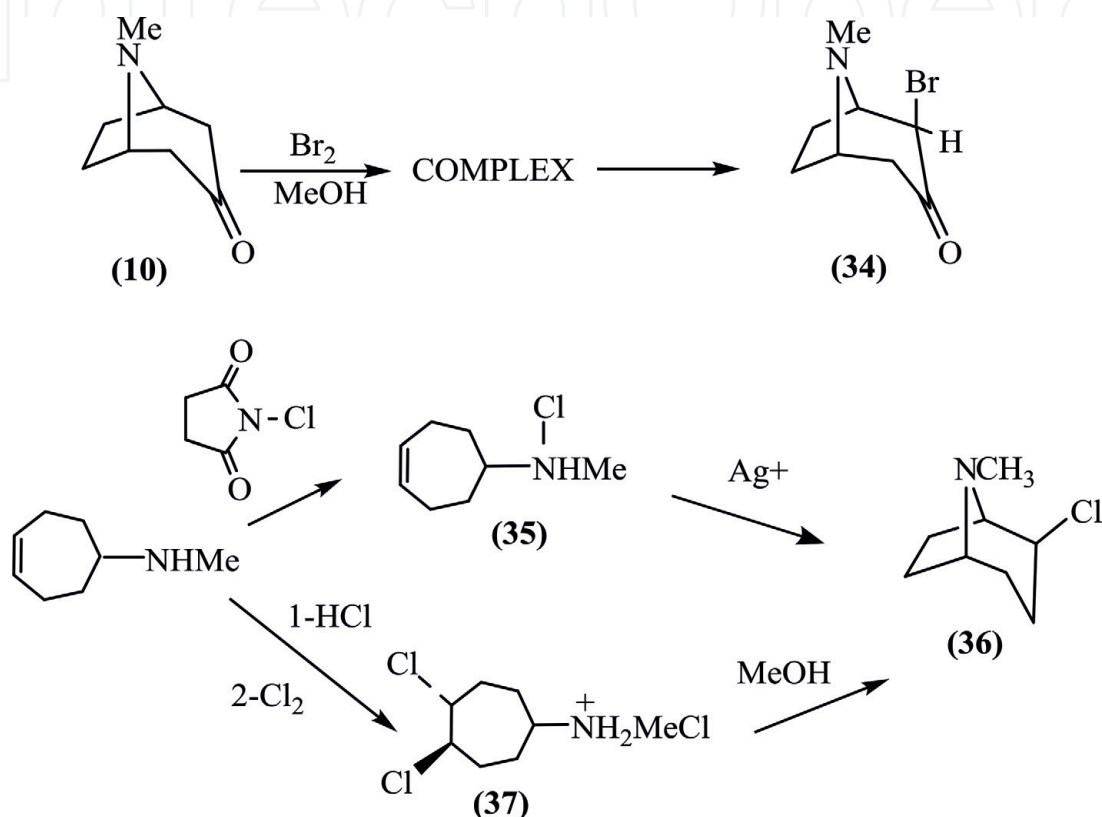


Figure 16.
 Synthesis of 2-bromo-3-tropanone (34) and the 2-chlorotropane (36).

Although tropan-2-one (18) appeared to be a very convenient synthetic precursor of both tropan-2 α -ol (30) and tropan-2 β -ol (25), the ketone itself was not easy to prepare. The ketone may be obtained in good yield from ecgonine (3) or cocaine (6), but these alkaloids are expensive. The alternative starting material used by Pinder and co-workers, 2-ethoxycarbonyl-pyrrole (26), is also expensive, and the subsequent synthesis was too long for it to be useful for the preparation of large amount of tropan-2-one.

2.2 Synthesis of tropan-2 β -ol (21) from tropinone (10)

Tropinone (10) was available in reasonable quantities and was chosen as a convenient source of tropane derivatives. Reduction of this ketone with borohydride gave a mixture of the epimeric tropan-3-ols (38), which were dehydrated to tropidine (21) by Landenburg's method [31] as it can be seen in **Figure 17**.

An allylic oxidation of tropidine (21) with selenium dioxide [32] to yield a β -unsaturated ketone (39) was an attractive prospect, but this could not be realized: there was no apparent reaction in aqueous dioxin after 50 hours on a boiling water bath. Other allylic reagents, such as *N*-bromosuccinimide or lead tetraacetate,

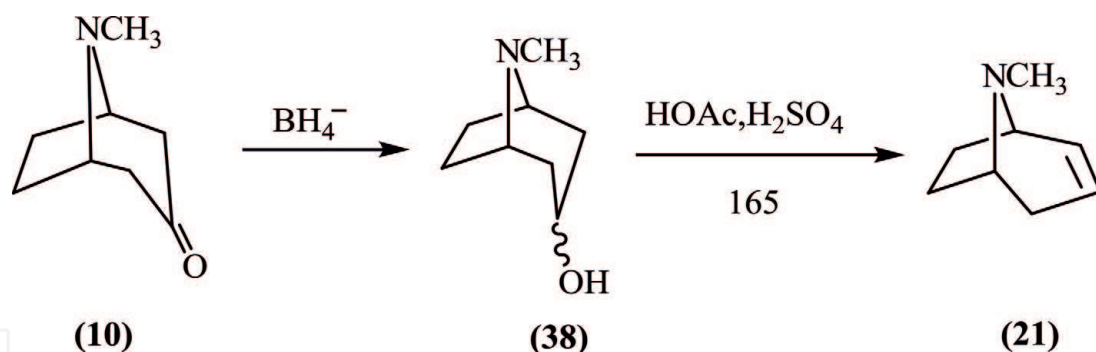


Figure 17.
Synthesis of tropidine (21) from Tropane-3-one.

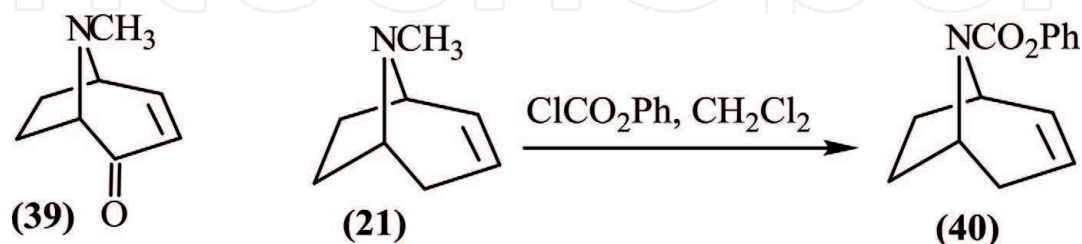


Figure 18.
Synthesis of the compound (40).

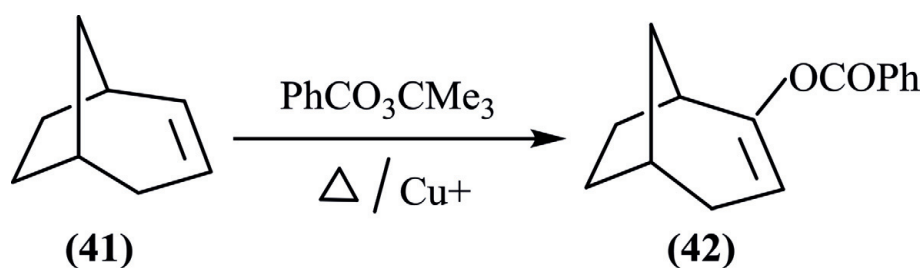


Figure 19.
Synthesis of the racemic mixture of (42).

would also be ineffectual in the presence of the *N*-methyl group, so that the most convenient method of protecting the nitrogen atom is provided by the reaction of tropane derivative with phenyl chloroformate [33]; thus, treatment of tropidine (21) with phenyl chloroformate in dichloromethane gave *N*-phenoxy-carbonyl-nor-tropidine (40) a good yield (**Figure 18**). The nitrogen of the urethane group is non-basic, and, furthermore, the *N*-methyl group can be regenerated by reduction of the urethane with lithium aluminum hydride.

Goering and Mayer [34] have reported that optically pure bicyclo[3.2.1]oct-2-ene (41) reacts with tert-butyl perbenzoate, in the presence of cuprous ion, to give racemic of (42) presumably via a symmetrical allyl radical (**Figure 19**).

Epoxidation of unreactive olefins with trifluoroperacetic acid is usually carried out in dichloromethane with phosphate present to buffer the trifluoroacetic acid that is a product of the reaction [35]. The epoxidation of *N*-phenoxy-carbonyl-nor-tropidine (40) by means of trifluoroperacetic acid was inconvenient for two reasons. Firstly, it gave a mixture of products, including a large proportion of unchanged olefin, which necessitated careful column chromatography of the mixture in order to obtain the required 2 β ,3 β -epoxide (43a, b) (**Figure 20**). Secondly, the peracid itself is inconvenient to prepare and is an unpleasant reagent. It has been reported that there is a simplified procedure for epoxidation, using a nitrile as a

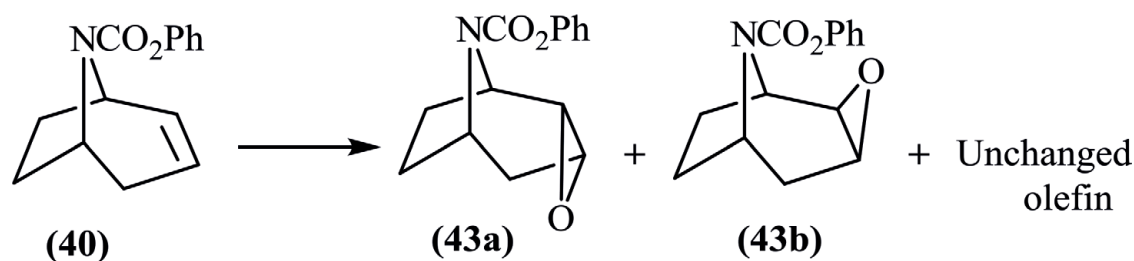
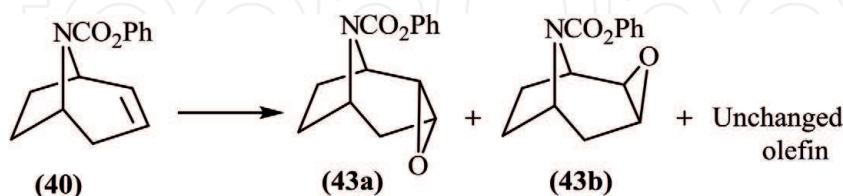


Figure 20.
Synthesis of the epoxides of (40).



Scheme (13): synthesis of the epoxides of (40)

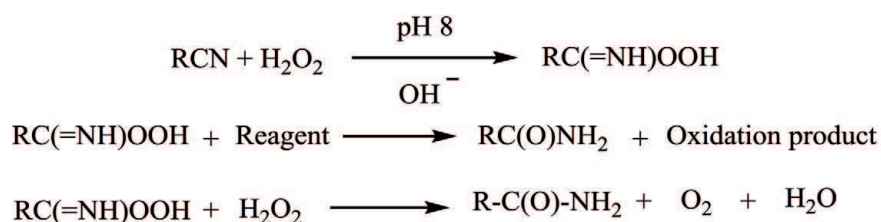


Figure 21.
Synthesis of peroxycarboximidic acid.

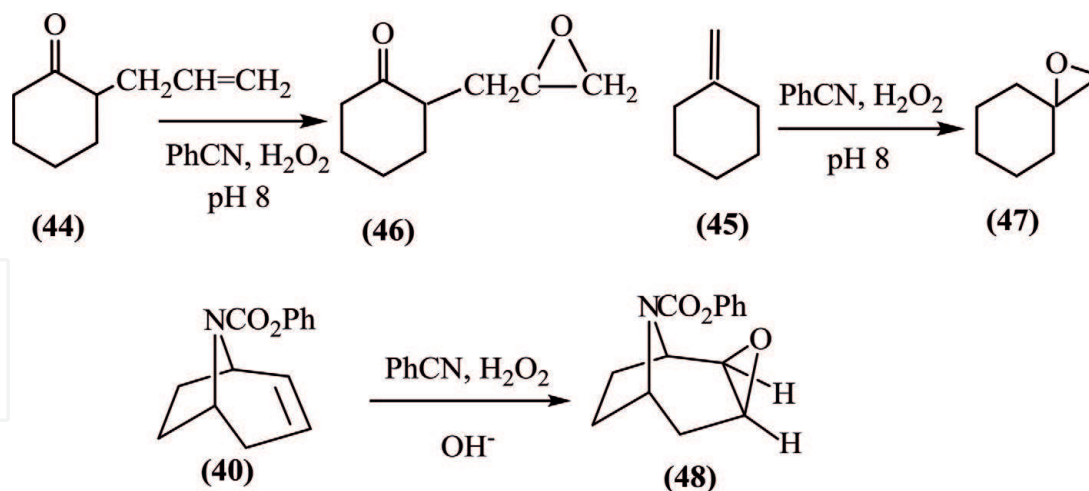


Figure 22.
Oxidation of some unreactive olefines.

reactant with hydrogen peroxide [36, 37]. The reaction occurs in weekly basic solution and is thought to involve a peroxycarboximidic acid $[\text{RC(=NH)OOH}]$, which is too reactive to be isolated. In the absence of a suitable reducing agent, $[\text{RC(=NH)OOH}]$ will oxidize hydrogen peroxide, the Radziszewski reaction [38] outlined in **Figure 21**. But in the presence of an olefin, the Radziszewski reaction may be eliminated and epoxidation effected [36].

For example, the epoxidations of (44) and (45) proceeded smoothly with benzonitrile and hydrogen peroxide to (46) and (47), respectively (**Figure 22**), whereas (44) was found to undergo Baeyer-Villiger cleavage with peracetic acid [41]. The

reaction of *N*-phenoxycarbonyl-nor-tropidine (40) with benzonitrile and hydrogen peroxide in weakly basic solution gave the expected 2 β ,3 β -epoxide (48). By the use of a large excess of reagents, a yield of 38% was achieved but could not be increased [39].

2.3 Synthesis of 2-(*p*-toluenesulphonyl) tropane-2-ene: anhydroecgonine analog

As mentioned earlier, molecules that contained tropane structure, for example, tropane (1), ecgonine (2), tropinone (3), and cocaine (4) or one of its fragments, show central stimulating effects [40–45], using them as anticholinergic agents [46, 47].

Much of the modification designs involved isomeric studies [48]. Most of the modifications came to the tropane moiety, the bridge nitrogen (N₈) [49], or modification at the C₂ position [50]. Many processes for synthesizing anhydroecgonine derivatives without using cocaine as a starting material have been reported in literature. For example, it was shown by Grundmann and Ottman [51] as well as Okano and Osamu [52] that the reaction of ethyl cycloheptatriene-7-carboxylate (49) with methylamine gave anhydroecgonine ethyl ester (50) (**Figure 23**).

Conversion of the corresponding carboxylic acid to tropane-2-one has been accomplished by Bell and Archer [53] in a four-step sequence involving conversion to the carboxamide and Hofmann degradation with sodium hypochlorite.

Because (49) was not readily available, Hobson et al. [54] as well as Okano and Itoh [55] developed a relatively inexpensive route starting with corresponding cyano-derivatives which is readily accessible by reaction of tropylium fluoroborate (51) with sodium cyanide to give (52). The nitrile (52) was reacted with methylamine in *t*-butanol to give the 2-cyano tropidine (53) in high yield (see **Figure 24**).

In our work on the 1,3,5-cycloheptatriene-2-ylphosphorus derivatives (54) and (55) (**Figure 25**), little success was achieved in obtaining isolable products from reactions with nitrogen nucleophiles, except in those cases, for example, pyrrole-2-aldehyde, where the presence of aldehyde group enabled the intermediate ylide to be trapped [56].

Investigation of the behavior of the 2-(*p*-toluenesulphonyl) analog in this type of reaction turned out to be more fruitful and provided a useful entry to 2-substituted tropanes, and in particular the rather difficultly accessible ketone, tropan-2-one. 7-(*p*-Toluenesulphonyl)-1,3,5-cycloheptatriene (56) was found to react smoothly with primary amines in dry acetonitrile under reflux to give adducts of general structure (57) in good yields, thus greatly improving the accessibility of compounds of this type [57]. When (56) was isomerized to (56a) in acetonitrile using 1,4-diazabicyclo[2.2.2]octane (DABCO) as a catalyst, and the latter was treated with methylamine in refluxing ethanolic solution, 2-(*p*-toluenesulphonyl)-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (57a) was obtained as a pale yellow oil in a yield of 80% (**Figure 26**).

Its mass spectrum showed a molecular ion peak at *m/e* 277, and the IR spectrum showed a band at 1600 cm⁻¹ characterizing the double bond. Identification of this compound was confirmed by the ¹H-NMR spectrum, which showed signals at δ 3.15

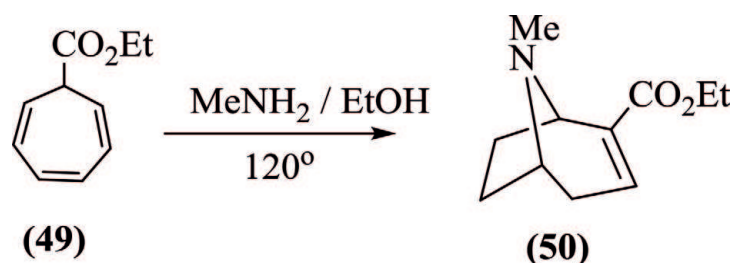


Figure 23.
Synthesis of anhydroecgonine ethyl ester (50).

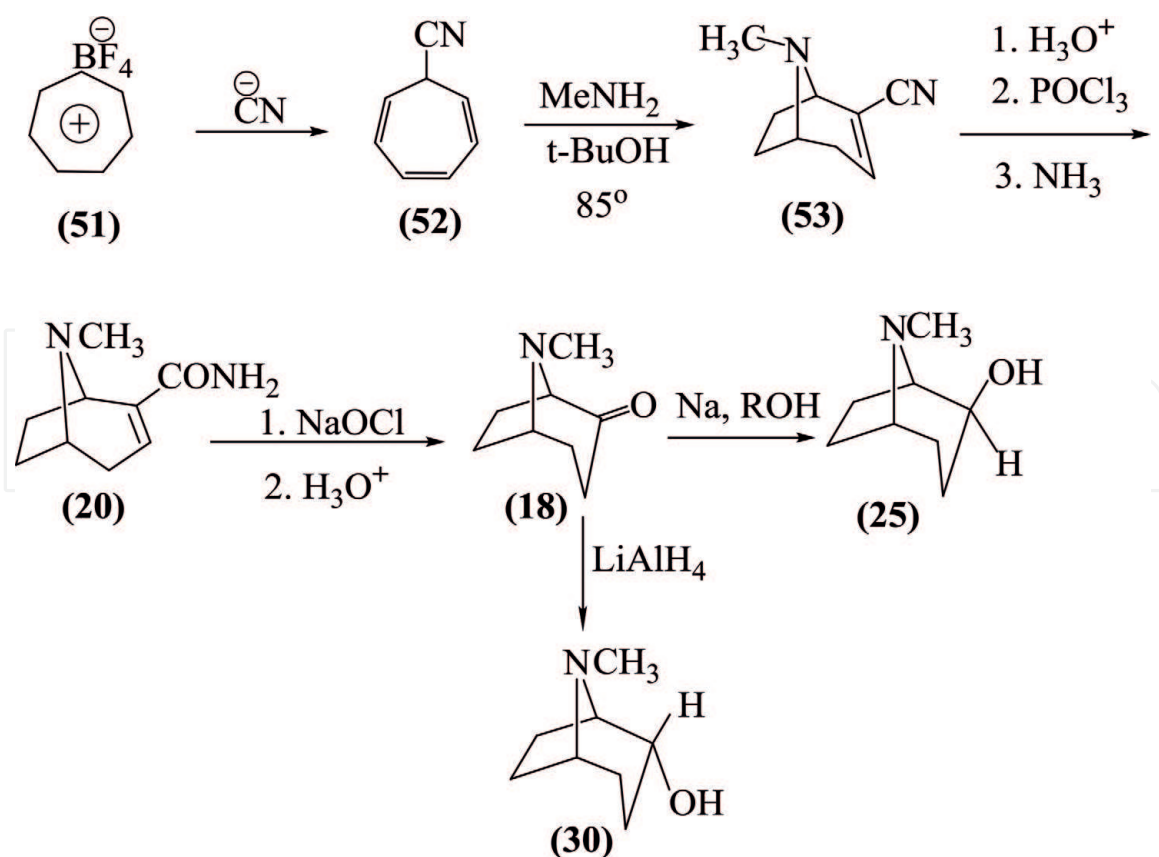


Figure 24.
Synthesis of the acetonitrile (52) and its conversion to (18).

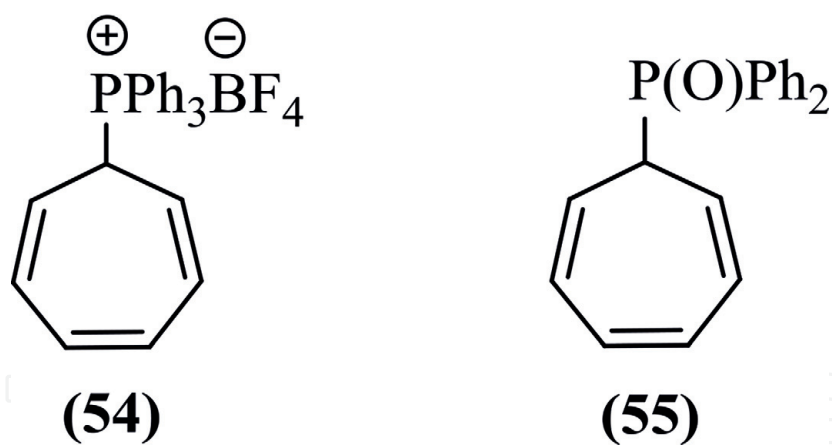


Figure 25.
7-phosphonium and phosphine oxide of cycloheptatriene.

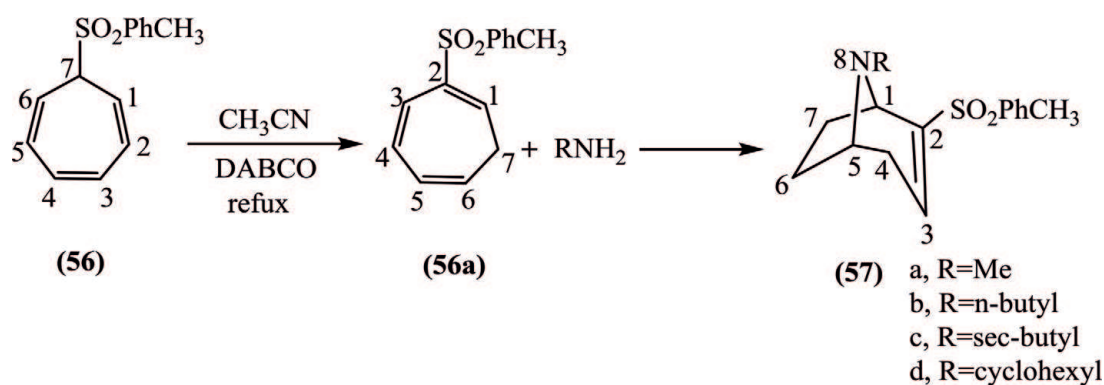
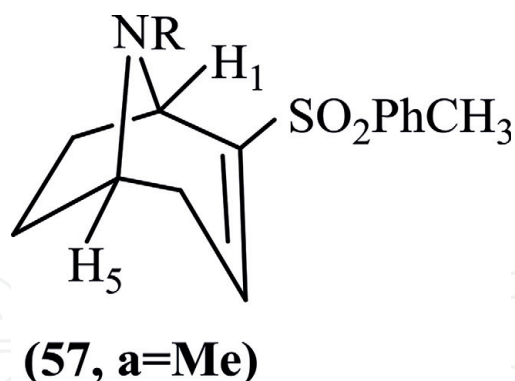


Figure 26.
Synthesis of 2-(p-toluenesulfonyl)-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (57a).

and 3.45 due to the bridgehead protons, H_1 and H_5 ; a 1-H multiplet at 6.82 as well as upfield protons between 1.2 and 2.8 ppm (see Structure 57, $a = \text{Me}$).



Similarly the sulfone (56a) was refluxed with an excess of *n*-butylamine in acetonitrile; TLC examination showed the formation of only one product. Isolation and recrystallization from hexane afforded white crystals of 2-(*p*-toluenesulphonyl)-8-*n*-butyl-8-azabicyclo[3.2.1]oct-2-ene (57b), mp, 119–121°C (85%). Mass (m/z 319) and IR and NMR spectra confirmed that the compound was (57b). Another example of this reaction involving addition of *sec*-butylamine to the sulfone (56b) also proved successful under similar conditions. 2-(*p*-tolylsulphonyl)-8-*sec*-butyl-8-azabicyclo[3.2.1]oct-2-ene (57c) was obtained in 41% yield as a colorless oil which partially crystallized on standing. TLC analysis of this product showed two inseparable spots for the diastereoisomers of (58) and (59) (Figure 27). The NMR spectral data included a multiplet at δ 0.6–2.20 as expected for upfield protons of (57c) accompanied by signals at 3.35, 3.60, and 6.85 ppm due to two bridgehead protons and one olefinic proton, respectively. The elemental analysis and mass spectrum (molecular ion at m/z 319) confirmed the structure. Also, the reaction of the sulfone (56a) with excess of cyclohexylamine in refluxing acetonitrile also gave a solid product in 75% yield 2-(*p*-toluenesulphonyl)-8-cyclohexyl-8-azabicyclo[3.2.1]oct-2-ene (57d). Its IR and NMR spectra were similar with those structures of (57a–c), and the structure was confirmed by the mass spectrum, which showed a molecular ion peak at m/z 345.

In the case of the reaction of (56a) with benzylamine, a slightly different result was obtained. The product was obtained as needles, mp 172°C, and elemental analysis, mass spectroscopy, and spectral data confirmed the structure (60) (Figure 28).

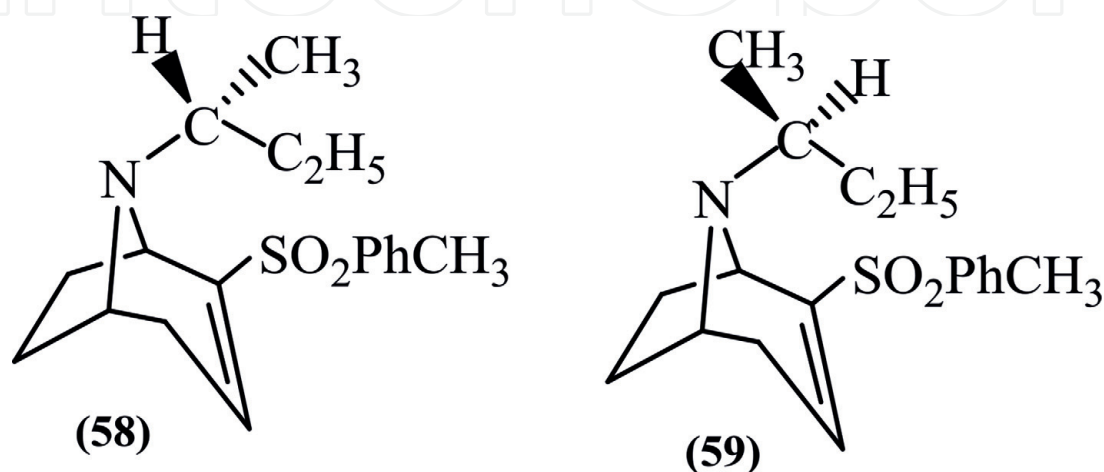


Figure 27.
The diastereomers (58) and (59).

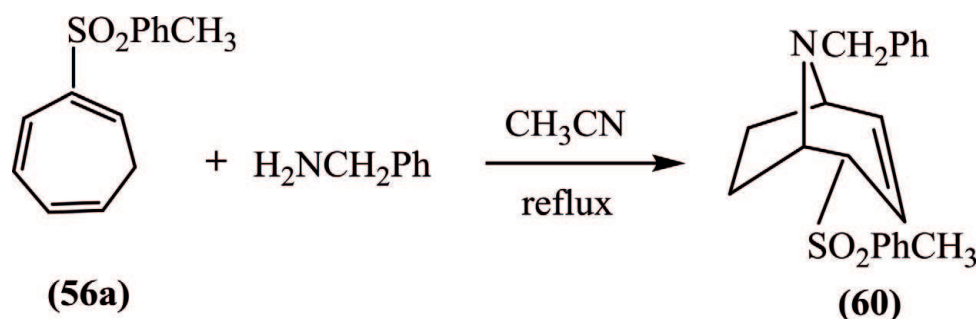


Figure 28.
Synthesis of compound (60).

The mechanism for the formation of compounds (57a–d) and (60) presumably involves in the first step of the Michael addition of the amine to C₁ of the sulfone (56a) to give intermediate compound (61). Further base-catalyzed isomerization gives the compound (62), followed by intramolecular Michael addition which would lead to the compounds (63a–d) and (60) (**Figure 29**). In the case of the compound (63a–d), further isomerization to the conjugated sulfone took place which was presumably facilitated by the presence of the strong bases, methylamine (pK_a 10.659), *n*-butylamine (pK_a 10.77), *s*-butylamine (pK_a 10.83), and cyclohexylamine (pK_a 10.66). The formation of the kinetically controlled product (60) in the case of the benzylamine reaction was presumably due to the weaker basicity of benzylamine (pK_a 9.35) which does not promote further isomerization. The same product was also obtained using acetonitrile as a solvent for the reaction. Cycloheptatriene was also obtained in the reaction mixture, presumably formed by slow decomposition of the sulfone (56a).

The total absence of 2-(*p*-toluenesulphonyl)-8-*t*-butyl-8-azabicyclo[3.2.1]oct-2-ene (65) in the products indicated that there was no nucleophilic attack on C₁ of the sulfone (56a) presumably because of steric bulk of the *t*-butyl substituent (**Figure 30**).

Attempts to react the sulfone (56a) with ammonia were unsuccessful; a solution of the sulfone (58a) in dry acetonitrile was refluxed and ammonia bubbled through for 24 hours. The only product to be isolated was a small quantity of what appeared to be, from its spectral properties, a pure toluene-*p*-sulphonamide.

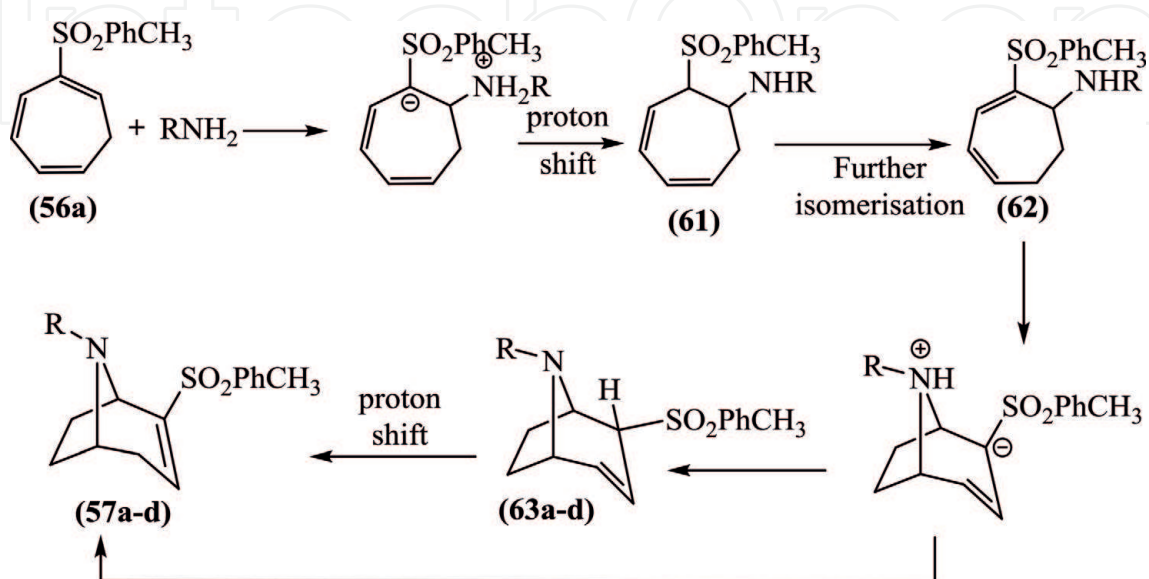


Figure 29.
Synthesis of 2-(*p*-toluenesulphonyl)-8-azabicyclo[3.2.1]oct-2-ene (57a–d).

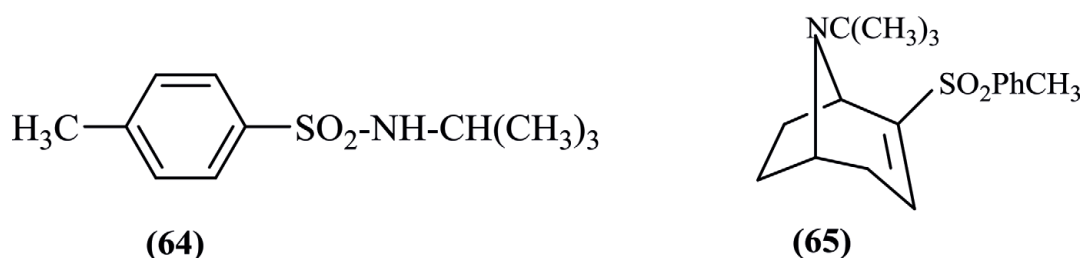


Figure 30.

Show the formation of compound (64) and absence of compound (65).

3. Conclusions


The tropane alkaloids made a great contribution to the history of medicine. Intensive research on chemistry and pharmacology of tropane alkaloids led to a fast development of pharmaceutical industries, particularly drugs that have anticholinergic effects. Since the first one-pot synthesis of tropane-3-one by Robinsons in 1917, several routes for synthesizing semisynthetic and synthetic tropane derivatives were published in literature. Chemical synthetic routes from different disciplines and field of research combined in this chapter, in an attempt to illustrate how through continual research, facilitate and develop synthetic chemistry of tropane derivatives. However, the synthesis of the famous tropane derivative, anhydroecgonine from 7-(*p*-toluenesulfonyl)-1,3,5-cycloheptatriene and amines, would provide alternative chemical procedure to people working in this field. This procedure has been shown to be simple, inexpensive research, and provide inspiration in the search for more tropane derivatives.

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